University of California, Los Angeles • School of Public Health
650 Charles E. Young Drive South, Los Angeles, California 90095-1772
Telephone 310-206-6920 • Fax 310-206-9903
Director: John R. Froines, PhD.

8/19/08:
1. CK

August 11, 2008

2. Ms. Mary-Ann Warmerdam
Director
Department of Pesticide Regulation
1001 I Street
P.O. Box 4015
Sacramento, California 95812-4015

3. Andrews
4. [illegible]
5. Segawa

Dear Ms. Warmerdam:

The purpose of this letter is to transmit the Scientific Review Panel on Toxic Air Contaminants' Findings on endosulfan. The findings were based on the Panel's review of the Department of Pesticide Regulation's revised draft report titled "Endosulfan Risk Characterization Document" (April 2008) prepared by your department's staff and reviewed by the Office of Environmental Health Hazard Assessment (OEHHA).

The Panel reviewed the draft report as well as the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based, as required by state law. The Panel also reviewed comments received and responses to those comments. In approving the report, it is the Panel's conclusion that the report, with the revisions requested by the Panel, is based on sound scientific knowledge.

The Panel recommends that you take the necessary steps to list endosulfan as a toxic air contaminant. While annual use has been declining, mainly due to reduced cotton acreage in the San Joaquin Valley, its moderate volatility and persistence properties enable it to persist in the environment resulting in populations close to or far from applied fields being exposed to endosulfan via the air.

The Panel differed from DPR scientists in two areas. The Panel and DPR scientists agreed to disagree, and any differences were entirely professional in nature. The interactions with your staff were especially positive and we

Findings of the Scientific Review Panel on Toxic Air Contaminants on the Proposed Identification of Endosulfan as a Toxic Air Contaminant, as adopted at the Panel's May 16, 2008 meeting

The Scientific Review Panel on Toxic Air Contaminants (Panel) reviewed the draft report, "Endosulfan Risk Characterization Document," prepared by the Department of Pesticide Regulation (DPR), along with findings prepared by the Office of Environmental Health Hazard Assessment (OEHHA), that propose to identify endosulfan as a toxic air contaminant (TAC). The DPR report is an evaluation of human health risks associated with potential human exposure to endosulfan and its degradation products (α- endosulfan, β-endosulfan, and endosulfan sulfate), and provides the basis used by DPR in considering whether to list endosulfan as a toxic air contaminant.

The Panel reviewed the initial DPR report in a meeting on September 26, 2007, and subsequently reviewed revised reports in meetings on December 4, 2007, and on February, 28, 2008. DPR submitted a further revised version of the document (dated April 2008) to the two Panel lead reviewers on April 3, 2008 and the entire Panel on May 2, 2008. As part of its statutory responsibility, the Panel prepared the following findings based on its review of the endosulfan risk characterization, which are submitted to the Director of the DPR.

1. Endosulfan is a broad-spectrum, non-systemic insecticide and acaricide used to control sucking, chewing, and boring insects on a wide variety of vegetables, fruits, grains, cotton, tea, ornamental shrubs, vines, and trees. There are six registered products in California that contain endosulfan as an active ingredient. Endosulfan is classified as a chlorinated hydrocarbon of the cyclodiene group. Endosulfan exists in α and β isomeric forms. The α isomer is a more potent inhibitor of chloride flux in nerve cells and has been found at higher concentrations in air monitoring studies.

2. Annual use of endosulfan in California has been declining, from 240,000 pounds in l997 to 83,000 pounds in 2005. This is mainly due to reduced cotton acreage in the San Joaquin Valley. Peak use of endosulfan occurs from June to September.

3. Between l992 and 2004, the Pesticide Illness Surveillance program of DPR recorded 63 illnesses that likely involved exposure to endosulfan. Of these, nine resulted from drift in the air following endosulfan application. Most of the illnesses were skin and/or eye irritation. Neurotoxic symptoms were reported in six applicators and in one nearby resident.

4. Endosulfan can be found in almost all media in the environment. It is moderately volatile. Its moderate adsorption and persistence properties enable it to persist in the environment for an extended period of time. Thus, populations close to or far from agricultural fields can be exposed to endosulfan via the air.

5. Persons near pesticide application sites are subject to high exposure to endosulfan via inhalation if the chemical drifts in the air into the area immediately surrounding the field (bystander exposure). ARB measurements near an apple orchard treated by airblast

application of endosulfan were used to calculate short-term (24-hour TWA), seasonal (3-day TWA), and annual (3-day TWA) bystander exposures.

6. Seasonal (one week to one year) and annual (one year) exposures via ambient air are estimated in the RCD/TAC document for the Seasonal Absorbed Daily Dosage (SADD) and the Annual Absorbed Daily Dosage (ADD). The Short-Term Absorbed Daily Dosage (STADD) was assumed to be equal to or less than the short-term bystander exposures.

Table 1. Seasonal and Annual Exposures to Endosulfan via the Ambient Air

	Infants	Adults
STADD, mg/kg-day	0.00160	0.00076
SADD, mg/kg-day	0.000037	0.000017
AADD, mg/kg-day	0.000021	0.000010

Short-term (up to one week), seasonal (one week to one year), and annual (one year) bystander exposures are estimated in the RCD/TAC document (Table 2).

Table 2. Short-Term, Seasonal, and Annual Bystander Exposures to Endosulfan

	Infants	Adults
STADD, mg/kg-day	0.00160	0.00076
SADD, mg/kg-day	0.00056	0.00027
AADD, mg/kg-day	0.000047	0.000022

7. The central nervous system (CNS) is the major target of endosulfan action. Endosulfan binds to the γ-aminobutryic acid (GABA)-gated, chloride channel receptor, resulting in inhibition of GABA-induced chloride flux across membranes. This is thought to be the primary mechanism by which endosulfan causes generalized brain stimulation and neurotoxicity in mammals. Hence, neurotoxicity is the primary effect observed in both acute and chronic exposure in humans and animals. Endosulfan is a strong neurotoxin in animals (rats, dogs, mice, cows, cats, goats, and sheep) and in humans. The liver and kidney are additional primary target organs for endosulfan-induced toxicity. In addition, effects of endosulfan on developing male reproductive organs indicate it is also a developmental toxicant. The subchronic inhalation NOAEL of 0.194 mg/kg-day is the critical NOAEL for evaluating both acute inhalation exposures and seasonal inhalation exposures in humans. The estimated no-effect level of 0.0194 mg/kg-day based on subchronic effects in animals is the appropriate value for evaluating chronic inhalation exposures in humans.

8. Endosulfan binds covalently to DNA to form DNA adducts in human liver cells and in rat hepatocytes, and induces DNA damage in mammalian cells, mutation, chromosomal aberrations, SCE, and micronuclei in vitro in mammalian cells, and sex-lined recessive lethals and sex chromosome loss in Drosophila melanogaster. Alpha and β-endosulfan and the sulfate, lactone, and ether metabolites of endosulfan inhibited gap junctional intercellular communication in cultured hepatocytes, and α-endosulfan also induced tumor promotion (altered hepatocyte foci) in rats. The Panel has concluded endosulfan is likely genotoxic. Endosulfan has not consistently induced tumors in rats and mice. However, due to its

genotoxicity and tumor promoting ability, endosulfan has the potential to be carcinogenic with further studies required.

Panel conclusions regarding endosulfan as a TAC

9. DPR calculated MOEs by dividing the appropriate NOAEL by the exposure. Short-term, seasonal and annual inhalation MOEs were calculated for infants and adults exposed as bystanders (Table 3). When using NOAELs from animal studies, DPR considers MOEs of greater than 100 to be health protective, regardless of the route of exposure. Specifically for inhalation exposures to the general public, MOEs of less than 1000 indicate that a chemical should be identified as a TAC.

Table 3. Margins of Exposure (MOEs) in the Volume I Health Risk Assessment document for Short-Term, Seasonal and Annual Exposures to Endosulfan via Bystander Inhalation Only, or via Bystander Inhalation + Dietary (i.e., Aggregate)*

	Infants	Adults
Short-term Inhalation MOEs	121	255
Seasonal Inhalation MOEs	346	719
Annual Inhalation MOEs	413	882
Short-term Aggregate MOEs	78	146
Seasonal Aggregate MOEs	296	595
Annual Aggregate MOEs	343	702

*** Adapted from "Revised Findings on the Health Effects of the Active Ingredient: Endosulfan," OEHHA, Table 4, February 25, 2007 at page 10.**

Inhalation MOEs ranged from 121 to 882. Adding in dietary exposure gave lower MOEs, ranging from 78 to 702. Infants had the lowest short-term aggregate MOE of 78. The Panel concludes all MOEs, both inhalation-only and aggregate, were below 1000, making endosulfan a potential TAC.

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10. Reference doses (RfC) were calculated by DPR (Table 4). Table 4 shows the MOEs for the exposure scenarios with the percent RfC. The percentage should be greater than 10% for the pesticide to be listed as a TAC. The Panel concludes all bystander scenarios exceeded the threshold for listing of endosulfan as a TAC.

Table 4. Estimated MOEs for Endosulfan in Bystander Scenarios and their Corresponding Percent Reference Concentrations*

Exposure Scenario	Infants		Adults	
	MOE	%RfC[a]	MOE	%RfC
BYSTANDERS – East Station				
Acute	121	82%	255	39%
Subchronic	346	29%	719	14%
Chronic	413	24%	882	11%

11. The Panel notes there is evidence for young rats being more sensitive to endosulfan than adults and there are toxicokinetics uncertainties. The Panel recommends that DPR apply an additional uncertainty factor of 3 to 10 in calculating the infant RFCs.

12. The Panel notes that animal tests identified dermal irritation from technical grade endosulfan. Endosulfan produced dermal and ocular irritation. The Panel concludes there is a possible risk of dermal sensitization in humans exposed to endosulfan.

13. The Panel has reviewed the scientific data on which the DPR report is based, the scientific procedures and methods used to support the data in the DPR report, and the conclusions and assessments of the DPR Report. The Panel concludes the DPR report is based on sound scientific knowledge and represents a valid assessment of our current scientific understanding.

14. The Panel recommends that the DPR Director initiate the necessary regulatory steps to list endosulfan as a Toxic Air Contaminant pursuant to section 14023 of the Food and Agricultural Code.

I certify that the above is a true and correct copy of the findings adopted by the Scientific Review Panel on Toxic Air Contaminants on May 16, 2008.

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John R. Froines, Ph. D.
Chairman
Scientific Review Panel on Toxic Air Contaminants

appreciate the back and forth that represents the best approach to the science of this compound. I cite them here for your consideration in any future risk management activities or possible requests for further testing by the National Toxicology Program. The Panel noted there is evidence in young rats being more sensitive to endosulfan than adults and there are toxicokinetic uncertainties. As a result the Panel recommends that DPR apply an additional uncertainty factor of 3 to 10 in calculating the infant RFCs.

The Panel also considered the evidence for genotoxicity to be sufficient to consider endosulfan a genotoxic agent with potential for carcinogenicity. The Panel was unanimous in recommending that further studies on the carcinogenicity of this pesticide would be appropriate.

Please extend to your staff the Panel's and my appreciation and thanks for their efforts to complete this report and for engaging the Panel in lively discussions to respond to questions and concerns.

We ask that the Panel's findings and this letter be made a part of the final report.

Sincerely,

John R. Froines, Ph.D.
Chairman
Scientific Review Panel on Toxic Air Contaminants

cc: Scientific Review Panel members

Joan E. Denton, Ph.D.
Director
Office of Environmental Health Hazard Assessment

Mary D. Nichols
Chairman
Air Resources Board

Jim Behrmann
Liaison, Scientific Review Panel

Enclosure: Findings of the Scientific Review Panel on the Proposed Identification of Endosulfan as a Toxic Air Contaminant